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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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735 8th Street, S.E.
Washington, D.C. 20003-2802
(202) 546-6666

PARTICIPANTS

Vincent H.L. Lee, Chair
Kathleen Reedy, Acting Executive Secretary

MEMBERS

Gloria Anderson, Ph.D. (Consumer Representative)
Judy P. Boehlert, Ph.D.
William J. Jusko, Ph.D.
Joseph Bloom, Ph.D.
Lemuel A. Moye, M.D., Ph.D.
Marvin C. Meyer, Ph.D.
Arthur H. Kibbe, Ph.D.

Industry Guests

Leon Shargel
Efraim Shek

Guests and Industry Participants

Gerry Migliaccio
Ken Lavin
Michael S. Korczynski, Ph.D.
Sandra A. Lowery, M.B.A., ASQ-CDA
Anne Marie Dixon
Berit Reinmuller, Ph.D.
Don Burstyn, Ph.D.
Jeanne Moldenhauer, Ph.D.
Terry Munson
Russ Madsen

FDA Speakers

Richard Friedman
David Hussong
Kris Evans
Robert Sausville
Brenda Uratani, Ph.D.

FDA

Douglas I. Ellsworth
Jay Elterman
Joseph Famulare
Ajaz Hussain, Ph.D.
Helen Winkle

at

C O N T E N T S

at

C O N T E N T S (Continued)

Manufacturing Issues Discussion

P R O C E E D I N G S

Call to Order

DR. LEE: Good morning. I am Victor Lee, Department of Pharmaceutical Sciences, School of Pharmacy at the University of Southern California in Los Angeles. I am the Chair of this Committee, the Committee for Pharmaceutical Science.

Let me begin by asking the folks around the table to introduce themselves. Ajaz?

DR. HUSSAIN: Ajaz Hussain, Deputy Direction, Office of Pharmaceutical Science.

DR. MOYE: University of Texas, Biostatistics.

DR. JUSKO: William Jusko, University of Buffalo.

DR. MEYER: Marvin Meyer, Emeritus Professor, University of Tennessee.

DR. KIBBE: Art Kibbe, Professor, Wilkes University.

DR. ANDERSON: Gloria Anderson, Callaway Professor of Chemistry, Morris Brown College.

DR. BLOOM: Joseph Bloom, University of Puerto Rico.

DR. BOEHLERT: Judy Boehlert. I have my own pharmaceutical business.

DR. SHARGEL: Leon Shargel, Eon Laboratories.

DR. SHEK: Efraim Shek, Abbott Laboratories.

MR. MIGLIACCIO: Gerry Migliaccio, Vice President of Global Operations from Pfizer representing PhRMA.

MR. LAVIN: Ken Lavin, Director of Regulatory Compliance with Teva Pharmaceuticals representing GphA.

DR. LEE: Thank you very much. Kathleen, are you ready? We are kind of short-handed this morning. Kathleen is going to read us the conflict-of-interest statement.

Conflict of Interest

MS. REEDY: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industry sponsors and academic institutions.

All special government employees and federal guests have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted waivers to the following special government employees which permits them to participate in today's discussions: William J. Jusko, Ph.D and Judy Boehlert, Ph.D.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant and guest. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We would like to note for the record that Dr. Efraim Shek of Abbott Laboratories and Dr. Leon Shargel of Eon Labs are participating in this meeting as industry representatives acting on

behalf of regulated industry. As such, they have not been screened for any conflicts of interest.

DR. LEE: Thank you, Kathleen.

I would like to begin the meeting by inviting Dr. Ajaz Hussain, Deputy Director of the OPS to give us the charge.

Future Subcommittee--GMP/Manufacturing

Introduction and Overview

DR. HUSSAIN: Good morning.

[Slide.]

I have prepared the presentation to talk about the Manufacturing Subcommittee that we proposed at a previous meeting and sort of lay out some details on that.

I also have a backup set of slides that I thought I could use to spend a bit more time to give all of our other FDA colleagues to get together because of the incident this morning. So I think I can spend some time explaining this in a bit more detail than I had originally planned.

[Slide.]

At a previous meeting, we had proposed to you that we would like to create a subcommittee on pharmaceutical manufacturing and that the PAT subcommittee would essentially sunset as this

complication sort of comes to become functioning.

Just to give you a sense, manufacturing, pharmaceutical manufacturing, is addressed by different parts of the Agency as it is done differently in companies, too. So we essentially are looking at the quality system which includes how do we set specifications to the test and controls and falling GMPs and then, also including, from a quality perspective, making sure the specifications make sense, are linked to safety and efficacy and then, when there are changes, how do you manage to insure that the product performance is unchanged.

So the quality system is quite a complex system with different parts of the Agency including a public standard-setting organization--that is, USP--that sort of comes to play in the overall quality system. So, if you start looking at it, how does each and every component work and how are these interlinked, I think it is time to take a hard look on that and see what improvements in the scientific foundation of this system can be done.

[Slide.]

So from the background perspective, pharmaceutical manufacturing is a very critical

component of the industry and it has to function as efficiently as it can to make sure the quality products are available to the U.S. public.

Manufacturing depends on R&D in developing optimal dosage forms. So I think the review part which we deal with, mostly R&D, has to set the specifications that are appropriate from a safety and efficacy perspective but also the specifications should be such that the manufacturability is considered appropriately.

So you are looking at R&D and manufacturing as two big clumps within the industry and sort of, in reflection to that, you have the review and inspective clumps, and how do these function, I think, is an important goal of understanding this so that we can do a more efficient job.

We started the PAT initiative about a year ago and that was with this in mind, how do you approve the science. That essentially has led to the new FDA initiative on cGMP for the 21st Century. So you have two major initiatives that are addressing pharmaceutical manufacturing in a global sense.

[Slide.]

The need for the Manufacturing Subcommittee was apparent to us even before we started the cGMP for the 21st Century initiative. So this Manufacturing Subcommittee we are proposing is to provide input and advice to CDER and FDA so manufacturing is not just Center for Drugs Review and Compliance, it is Office of Regulatory Affairs, and so forth. So this committee will have a much broader focus and input to the entire FDA in many senses.

Our original plan was to use this Manufacturing Subcommittee to bring input to FDA on science-based CMC and GMP policies. But, keeping in mind the broader scope, and the sunset of the PAT Subcommittee, we would also like this committee to focus on providing input to us on continued development of the PAT initiative.

Keep in mind, the PAT initiative with the subcommittee leads to a general guidance, but there will be need for many technical guidances that will have to be developed in this area and we will look to this committee for input on those issues.

Clearly, the cGMP for the 21st Century, a risk-based approach, will benefit from a lot of the discussions that can occur at this subcommittee.

So that is the thought process as to the scope of the subcommittee. It would range from very focused discussion on some topics. One example is the aseptic manufacturing discussion we have this afternoon to a broader discussion on other issues, too.

[Slide.]

We plan to model the Manufacturing Subcommittee after the PAT Subcommittee. It think the PAT Subcommittee was, in my mind, a very successful subcommittee that, with three meetings, gathered all the expertise and brought information to the FDA to help us write the draft guidance. Tomorrow is the last meeting, in once sense, of the PAT Subcommittee.

What we have learned from that is if you identify the right individuals who have the scientific expertise, it really helps to sort of crystalize the process very well.

Based on that sort of experience, what we are proposing is we will have a set of core membership, which is based on expertise in manufacturing and quality assurance to be part of this subcommittee. Some members of the PAT Subcommittee will be invited to participate as the

PAT Subcommittee sunset, so you will have continuity built in.

Then, once we have the core membership, we will have focused working groups or fact-finding groups which will sunset their activities after they have done their job. So this will be fluid working groups and fact-finding groups which will be assigned the task. Once they have completed it, they will sunset their activities and the entire group will focus on other areas.

Since the cGMP for the 21st Century has many immediate steps outlined, initial topics that we may need to focus on under the subcommittee may be some selected immediate steps outlined in the cGMP for the 21st Century Concept Paper. That is one of the possibilities.

[Slide.]

Here what I thought I would do is take a step backward and sort of look at the 21st Century Concept Paper that we have distributed to you and share some more information about this initiative. There were many drivers that led to this initiative and what we have seen over the last two decades is increased numbers of pharmaceuticals and their greater role in healthcare. In fact, several years

ago, the cost of drugs exceeded the cost of hospital care. So, the importance of medicines or drugs in healthcare is tremendous. At the same time, over the last decade, we have seen a decreased frequency of inspections. There are many reasons for that.

Also, we have been accumulating our experience in lessons learned from various approaches to product quality but we have been doing that in segments. It is now time to take a step back and sort of look at the entire system and make sure the connections are there.

Clearly, there have been advances in pharmaceutical scientific and manufacturing technology. Although we have brought some of these in on a step-by-step basis, it is again time to sort of look back and see how do we bring all of this into a complete system.

Application of biotechnology not only for drug discovery but also for drug development and for manufacturing--there are a lot of lessons to be learned from that. Clearly, there have been advancements in science and management of quality, itself. That revolution, the quality revolution, I think we can learn a lot from that. Clearly, we

are looking at a global industry rather than just the U.S. industry, itself.

[Slide.]

The pharmaceutical cGMP for the 21st Century essentially describes that initiative as a science- and risk-based approach to product-quality regulation incorporating an integrated quality-systems approach. That is sort of the basic foundation of this initiative. It is intended to incorporate a more up-to-date concept of risk management and scientific advances, encourage innovation and continuous improvement, ensure that submission review and cGMP inspection are coordinated and are synergistic and also ensure we have consistency and effective utilization of our resources.

So, in many ways, when you look at the title, the title is a bit narrow and I think the scope of this--in my mind, the correct title would be a drug-quality system for the 21st Century instead of cGMP. It is an entire system that we are looking at.

[Slide.]

The guiding principles that we have developed for this initiative are several. We will

have a risk-based orientation, science-based policies and standards, integrated quality-system orientation, international cooperation. Clearly, the strong public-health protection is always the foundation on which we will base all this on.

[Slide.]

We have outlined several steps. We are in the process of performing an external review of our existing cGMP programs and product-review practices including evaluation of potential inconsistencies in the implementation, reassess and revaluate our scientific approach to both the product-review process and cGMP program to achieve a consistent integrated-systems approach to product-quality regulation, enhance the scientific approach of cGMPs to emphasize risk-based control-point analysis and to facilitate the latest innovation in pharmaceutical engineering.

Those are the sort of broad steps that we have outlined.

[Slide.]

We have set for ourselves some immediate steps. An immediate step means we would have some results within six months. February is the deadline we are looking at. It doesn't mean we

will implement all that. We will have developed our understanding and our plans to a degree that we can actually start presenting some of these immediate steps to the stakeholders.

Among the immediate steps which I think will be the focus of some of our discussions in the subcommittee, holding scientific workshops with key stakeholders, enhancing expertise in pharmaceutical technology; for example, pharmaceutical engineering and industrial pharmacy by additional training and hiring and by leveraging external expertise, encouraging innovation within the existing framework by allowing certain changes in manufacturing processes without prior review or approval; for example, use of comparability protocols.

So I believe those are the main topics that we might start out in the subcommittee.

[Slide.]

But, there are other steps which may not be directly linked to the subcommittee activities which may include evaluating the optimal mechanism for effectively and efficiently communicating deficiencies to industry including content, consistency, disclosure and education; shifting the

Agency lead on implementation of Part 11 to CDER--that has already occurred--with continued involvement from other centers in ORA; including product specialists as needed as part of the inspection team

[Slide.]

Having centers provide a scientific and technical review of all drug cGMP warning letters; developing a technical dispute-resolution process that integrates technical experts from the Centers and addresses perceived inconsistencies between Centers; emphasizing a risk-based approach in the work-planning process and improving the operation of Team Biologics.

[Slide.]

The way we are moving forward is we essentially have created a set of working groups and a GMP Steering Committee. This is just to show the number of working groups active that are focused on the initial short-term milestone which is six months or less. We have a group on Contract Management, International Activities, Part 11, Dispute Resolution, Warning Letter Review, 483 Communications, Changes without Prior Review, Product Specialists on Inspection Team, Working

Planning and Risk Management, Cadre of Investigators, Developing Science Aspect, Evaluation of the Initiative, itself, and Quality Systems.

We have not started working on a Training Program at this time.

[Slide.]

SO, with that sort of a backdrop, I just wanted to share some thoughts on what the Manufacturing Subcommittee might take up as initial topics. Potential discussion topics, as examples, could include, I think, starting with Definitions and Common Understanding. What do we mean by a risk-based approach in the context of manufacturing. I think we would need to start discussing and sort of building a common consensus on what does risk constitute or in the context of manufacturing, what does that mean?

What do we mean by an integrated-systems approach? What is meant by a science-based approach? We have always been a science-based agency but what is different now? Science of quality? What is that and what is modern quality thinking, and so forth?

So these are some examples of the words we

use but which may have different meaning to different individuals and we need to have some common understanding.

[Slide.]

Just to give you sort of my way of looking at some of these words, if I go to Webster and pick up the definitions which I think apply. First, art; the power of performing certain actions, especially as acquired by experience, study or observations.

What does empirical mean; relying on experience or observation alone often without due regard for system and theory. What is science; accumulated and accepted knowledge that has been systematized and formulated with reference to the discovery of general truths of the operation of general laws.

[Slide.]

What is a system: a regularly interacting or interdependent group of items forming a unified whole; an organized set of doctrines, ideas or principles usually intended to explain the arrangements or working of the systematic whole marked by thoroughness and regulatory. What do we mean by risk; risk is the possibility of loss of

injury but also the degree of probability of such loss.

Clearly, I think we have to distinguish between possibility and probability and how do we sort of bring that into focus.

[Slide.]

But, at the heart of the whole debate, I think, what is quality and what is modern quality thinking? Here is some sense of that from eight quality gurus who have tried to define quality.

At the first level, quality is producing products or delivering services whose measurably characteristics satisfy a fixed set of specifications that are usually numerically defined. That is what quality is.

But, at level 2 it is customer satisfaction. In the modern way of thinking in terms of risk, I tend to look at FDA's role in this arena as a surrogate customer for our patients. We are the surrogate customers that have to be--I think satisfying our expectations leads to sort of a risk reduction and so forth. So that would be the sort of debate and discussion that we could have.

[Slide.]

More specific examples of topics that can be brought to this committee include approaches for enhancing the scientific basis of regulatory policies. We can pick topics and have focused discussion and this afternoon, I believe, would be one such example.

Regulatory approaches regarding aseptic manufacturing; I think our goal here is to ensure a sound scientific basis for cGMP inspection practices. The discussion this afternoon will be lead by our GMP colleagues. We haven't seen Joe yet--oh; Joe is here. I was trying to drag on, Joe, to make sure you were here. Joe Famulare will take the lead on the discussion and sort of bring to you their perspective on what are the important aspects here. I am hoping you would give them feedback in terms of how do you focus on science and making sure it is sound scientific basis and not simply going through a process where we have a "check box" exercise.

Science-based risk assessment and management, and so forth. But, also, I think, one opportunity here is to bring controversial topics such as general unresolved scientific technical disputes between industry and FDA. This would be

different from dispute resolution on a company-by-company basis but sort of bring more general issues here.

[Slide.]

What I would like to do; we have invited two guests, Gerry Migliaccio, who will represent PhRMA and Ken Lavin will represent GphA. After you listen to their perspective, if you could give us some input on what our goals and objectives of the subcommittee should be, the process that we have proposed--that is, have a core member group, two members from this advisory committee, maybe eight to ten expert participants representing stakeholders and then use the concept of fact-finding groups or working groups and how would we evaluate the success of this subcommittee.

So I will invite Gerry Migliaccio to sort of share PhRMA's perspective and then the GphA perspective and then your thoughts.

Thanks.

Industry Perspective

PhRMA

MR. MIGLIACCIO: Good morning. Thanks, Ajaz. I would like to thank the committee for inviting me to represent PhRMA to discuss to

proposed Manufacturing Subcommittee. I won't be using slides because they would probably be identical to Ajaz's. We have run into this at many meetings recently.

But PhRMA is extremely optimistic about the FDA's GMP initiative which Ajaz had just outlined. It is a positive step forward in the creation of what we have been advocating which is science-based GMP standards. It allows both FDA and industry to refocus their GMP compliance activities on what is important for fitness for use of the product. So, in other words, it allows us to focus our efforts on the patient.

This committee has been instrumental in promoting process analytical technology. That technology and other innovative technologies that are emerging in the pharmaceutical-manufacturing business have the potential to provide us with significantly more knowledge about the products and processes that we produce and that we use and have the potential to enhance quality assurance.

Now, if you combine those innovative technologies with science-based GMP standards, we truly have revolutionary potential in quality assurance in this industry. But, as in any case

when you have revolutionary potential, it needs to be harnessed, it needs to be guided properly.

I believe that this Manufacturing Subcommittee can play a significant role in guiding efforts around the GMP aspects, particularly the science-based GMP standard aspects of this initiative.

In particular, I believe it will allow both FDA and industry to leverage their resources and to focus them on those things, again, that are critical to the fitness for use of our products.

There are four specific areas where I think the subcommittee can make a significant impact on the GMP initiative. The first area; there will be many opinions about what is most critical in the area of science-based standards. From a PhRMA perspective, we believe that aseptic-manufacturing practices are crying out for science-based guidance.

Other people will have different opinions. This Manufacturing Subcommittee should serve as the steering committee to identify what the most important areas are for science-based standards and to prioritize the work on those. Whether that work is to done at PQRI or elsewhere, someone will need

to prioritize that work and I believe that Manufacturing Subcommittee is the right place for that to be done.

Secondly, as Ajaz talked about risk and risk-based approach, there are going to be many views. There are many views today on what risk-based means, both risk-based GMP compliance and risk-based CMC review. The subcommittee can provide the manufacturing and the quality-assurance perspective on risk-based in the context of those two, the GMP compliance arena and the CMC review.

Again, there will be many other perspectives on that. The common denominator to all those perspectives, again, is fitness for use. But I believe that this subcommittee can perform an important role in bringing together the perspectives of the manufacturing community and the quality community on what mean by risk-based.

The third area, which is--again, Ajaz talked about dispute resolution, what we are mostly calling technical-issues resolution; the subcommittee can play a significant role in the technical-issues resolution process that FDA is currently developing, not as the key player in resolving the issues between a firm and the FDA.

There needs to be an entire process developed for that.

But, just as in pharmaceutical manufacturing, you cannot address a problem or a deviation on its own. Yes; you deal with that deviation but then you have to step back periodically and do a trend analysis where the recurring issues that are cropping up not just in that area but industrywide. So not just with one firm but what is cropping up on an industrywide basis, what are the common issues that we are seeing come into this technical-issues resolution process.

In the early stages of the GMP initiative, the subcommittee evaluating trending what is happening in the technical-issues resolution process is going to identify the need for science-based standards. As we move on and mature in our science-based GMP standards, the trending of what is happening in the technical-issues resolution process will allow the subcommittee to clarify standards, to modify standards as required to meet the needs of what is occurring out there. So I think there is a significant role in that process for the manufacturing subcommittee.

Finally, the subcommittee should continue the work, really the model, that has been set by the Process Analytical Technology Subcommittee. It should serve as the vehicle for the introduction of new technologies in the pharmaceutical manufacturing sector.

There are perceived hurdles. There are perceived regulatory hurdles to introducing new technologies in pharmaceutical manufacturing. Some of those hurdles are valid. Some of them are not. But what there is not today is a forum for addressing new technologies on an industry-wide basis and on an agency-wide basis. The Manufacturing Subcommittee can serve as that forum to evaluate and enable.

The FDA has strongly stated that they do want to enable the introduction of new technologies and this Manufacturing Subcommittee can ensure that they are enabled.

This subcommittee has to have the appropriate expertise to achieve those four roles that I believe it should play. It should have, obviously, the best minds of FDA in this arena but it should also have a broad base of industry representation to ensure that all perspectives are

heard and are provided to the debate.

Representatives from innovator firms in the traditional drug-product sector, the biotechnology sector as well as in the active-pharmaceutical-ingredients sector should participate in this endeavor. PhRMA members stand ready to serve on the committee and we are very supportive of its mission, and we highly endorse the proposal.

Thank you.

DR. LEE: Thank you very much.

Are there any questions? If not, we have Ken Lavin to speak about the GphA Perspective.

Industry Perspective

GphA

MR. LAVIN: Thank you and good morning. On behalf of the GphA, I would like to thank you for allowing me to speak to you regarding this important initiative to enhance the GMP. We believe this program is an important step in clarifying industry's requirements in providing safe, effective as well as affordable pharmaceutical products to the American public.

[Slide.]

We currently believe there exists a wide

array of opinions and actions on the part of the Center and the field on various GMP topics. These opinions and actions also vary from district to district. It is costly for firms to be constantly addressing divergent thinking on these items. One voice and one set of actions by the FDA would further the ability of our companies to address the concerns of the agency.

Inconsistency in inspection and review has let firms to make the most conservative decisions and these may not necessarily be the best decision. This thinking is also limiting to our abilities to add and utilize technologies.

To ensure consistent interpretation and utilization, we believe that the publication of guidance documents will enhance overall compliance and provide clear direction to the industry.

[Slide.]

Some of the areas or topics that we feel should be discussed and the proper guidance provided for are, but not limited to, cleaning validation, process validation, training and vendor qualification.

[Slide.]

Cleaning validation; what is the level of

cleanliness desired? Clarification and true guidance on the use of the matrix approach to cleaning validation is needed. Technologies exist that can monitor and ensure a clean until clean approach. This approach is currently frowned upon. Firms cannot possibly address all the concerns of the Agency without clear guidance on this topic.

In light of the PAT initiative, we urge the FDA to consider this topic in a review of the currently Cleaning Validation Inspection Guidance.

[Slide.]

Process validation; currently firms expend a great deal of time and expense validating their processes. We feel that, while validation is necessary, the information gleaned from these programs could and should be used to lessen the burden on future manufacturing.

This information could lessen our in-process testing regimen. Further, validated process should allow a firm to eliminate unnecessary testing such as blend-uniformity testing.

[Slide.]

Personnel and the training they receive dictate the outcome of many processes. We believe

that the defining document describing the requirements for training and the documentation and tracking of the training all personnel receive is needed. Further clarification on these topics will enhance our abilities to provide the pertinent and up-to-day training our employees require.

Vendor qualification; our vendors of active and inactive ingredients provide us with the materials we need to manufacture quality products. These suppliers are also subject to the same regulatory and inspectional requirements as the finished dosage for manufacturers.

We believe that a guidance document on the qualification of these vendors that allows us to use these supplies and materials with a reduced testing program is warranted. This will allow us to use these materials without adding costs when the majority of the tests needed to release this materials for use have already been performed by qualified manufacturers.

By providing industry with the guidance documents, we believe that the goal of protecting the American public in providing safe, pure and effective products is assured. Industry cooperation and input into these guidance documents

is paramount to the success of this program. Inspection and review based on these documents will provide consistent compliance and provide our industry with the needed information to provide these products.

[Slide.]

The GphA looks forward to continued dialogue on these subjects and supports the endeavor of providing these guidances. We do have members that will sit on any subcommittee as needed.

Thank you.

DR. LEE: Thank you very much. Any immediate questions?

DR. HUSSAIN: I want to introduce Doug Ellsworth who is the District Director from the New Jersey District and Joe Famulare who is the Director of Regional Manufacturing and Product Quality.

DR. MOYE: I believe I understand what vendor qualification is and training. Process validation, I probably need some help on, but I can figure that out. But I don't know at all what cleaning validation is. Can you tell me what that is, please?

MR. LAVIN: Would you like me to answer that?

DR. MOYE: Please.

MR. LAVIN: Cleaning validation is assuring that any material that remains from a previous product and equipment is removed prior to introducing new materials into that equipment. That is done by swabbing or rinsing and then testing the rinse aid or the swabs for the presence of the previous materials.

DR. MOYE: Just to further parade my ignorance, there is no acknowledged industry standard for that; is that right?

LAVIN: No; there is not. There exists a guidance to inspections on cleaning that gives vague references to 10 parts per million or one one-thousandth of a dosage unit, but there are many interpretations by different firms as well as different investigators on what exactly is cleaning.

DR. MOYE: So there is guidance.

LAVIN: Well, there is not really. There are suggestions to guidance. It is not really a guidance document. It is a guide to inspections. It is an FDA internal--

DR. MOYE: I see. So there is not even guidance.

MR. ELLSWORTH: No.

DR. MOYE: When the FDA carries out its inspections, does it find wide variability in cleaning either procedures or cleaning goals? There is no common calibration for cleaning?

MR. FAMULARE: That's correct.

DR. MOYE: Thank you.

MR. FAMULARE: This is an observation that comes up from time to time and there are variations from company to company. I don't have any statistical answer to give you that X number of companies have X number of problems, but it does run the gamut from trying to get down to certain parts per million when going from one process to the other to the extreme where we find API facilities that are manufacturing chemical materials on the same processing equipment as APIs that are intended for human use.

So there is an extreme of findings there.

DR. LEE: Any other questions before we go into the committee discussion?

MR. ELLSWORTH: One comment I would like to make in terms of cleaning-validation guidance.

There are inspection guides, but I think it comes down to the science of how clean is clean. I know there are a number of publications that use different criteria but I think, for investigators in the field, looking at that is whatever scientific justification the term has.

I don't know if FDA has specific, or doesn't have a specific guidance on what should be followed in terms of how clean is clean.

DR. LEE: I think we will come to that later on this morning.

Committee Discussion

DR. LEE: OPS has posed a number of questions for the committee to discuss. I wonder whether we can put this up on the screen again.

[Slide.]

Those are the questions, the goals and objectives, the process and evaluation.

Art, you have been very quiet this morning.

DR. KIBBE: Thank you, Vince. Am I supposed to have an opinion?

DR. LEE: Yes. You always have an opinion.

DR. KIBBE: I had a question for Ajaz. I

was going to catch him afterwards, but, since you put me on the spot. On your third immediate step, it says here, "Having Centers provide a scientific and technology review of all drug cGMP warning letters." What does that really mean?

DR. HUSSAIN: It is a process that we are looking at in terms of issuance of warning letters, having Center input into that more so than we do now.

MR. FAMULARE: I think the real difference in that is, back in 1990, when warning letters began as an entity, they took over from regulatory letters. All regulatory letters were reviewed by a Headquarters unit, whether it be CBER, CDER, CVM. When we want to the warning letter, one of the issues about the issuance of the letters was the efficiency in time and processing them.

We found that it very often took so much time before the letter went through so many levels of review that it wasn't timely. So, direct reference was given to field officers such as Doug Ellsworth's New Jersey District and the nineteen other districts to issue warning letters on GMP deficiencies for dosage-form products.

There are some other examples, but that is

the primary one. What the GMP for the 21st Century is looking at is to--actually, a decision has been made to bring those letters back into Headquarters for technical review, review for consistency. The process is ongoing now to look at doing that and to have the proper resources in place.

DR. KIBBE: When I read it, I was concerned about going back to the situation where it took seven years to get a warning letter out on--I am exaggerating, of course. The understanding I had about warning letters is it was a way of getting the industry to recognize that there was a problem and to get it fixed quickly to minimize the time between an inspector recognizing the possibility of a problem that might impact quality and the industry responding to it so that that window was narrow.

When I read this, I started thinking about that window getting wide again.

MR. FAMULARE: Exactly. We are aware of the balance that we have to strike there to make sure that we get them out quickly. We have to put a system in place that, if we are going to have Headquarters review, we have to do it in a way that they are done quickly or we will not be able to be

effective with them.

But the idea of bringing them into Headquarters review is, again, to promote consistency and technically correct GMP points. That is not to say that all warning letters have those issues, but issues have been brought to light in terms of what one district says versus this other. So we are looking at it from that standpoint.

DR. KIBBE: Just a small aside. I think it is admirable to try to get warning letters as correct as possible before they go out. I would encourage that the Center people spend time educating the inspectors in a way that they share information so that they become comfortable with allowing the inspectors and the field people go to ahead and continue to issue warning letters.

I think we are better served, in a way, to push authority down if we have confidence in the people we are sending out in the field. It kind of sends the message that the Centers aren't confident that the people who are doing the inspections can do a quality inspection and send out a quality letter.

Do you know what I mean?

MR. FAMULARE: I wouldn't take it as a lack of confidence in the field. The important thing is to be able to have proper airing for those difficult or highly technical issues that sometimes need additional input. We want to be able to have the opportunity to provide that.

Doug can address, at the field level, how important it is to get that level of confidence as well with continued hiring and so forth.

ELLSWORTH: I think the issues relating to the warning letter, it is a bigger issue and we are working on improving the communication between technical experts that may be in the Center or elsewhere and the field so that we do have even stronger consistency in our inspectional process even before we get to that warning-letter stage.

DR. LEE: Let me bring the discussion back to the charge to this committee which is to discuss the goals and objectives. I would like to remind the committee that this subcommittee is patterned after the PAT Subcommittee which is now being sunset.

Those of us who were here yesterday and heard the presentation and, at least from our perspectives, the PAT Subcommittee seems to work

quite well. I would like read the slide that Ajaz showed. It is about the science and risk-based approach to product-quality regulation in cooperating an integrated quality-systems approach.

I just want to hear from the committee how you feel about the goals and objectives. Do you have any strong opinions, any advice? Yes, Leon?

MR. SHARGEL: I am in full agreement that the subcommittee is a good idea and science-based guidances and approaches to GMPs is appropriate. I would like the subcommittee to consider something that Mr. Lavin brought up, the level of testing.

In my experience, it is easier to add tests in the field than to take away a test, and to be examining what tests are really necessary. Are we testing too much or are we testing in the right places. As this is evolving, what is the most appropriate way of reaching good-quality products in manufacturing.

DR. LEE: Thank you.

Judy?

DR. BOEHLERT: I would also like to add my support to the concept. I think we heard from DPHA and PhRMA that there is a need for guidance documents. Although they had different areas that

they were focussing on, one on process validation, cleaning validation, the other on PAT and aseptic processing.

Clearly, the need exists. I think the challenge for the committee is going to be to gain consensus on some of those issues because there is a dichotomy between those that want a lot of guidance and those who want to be told what to do but not necessarily how to do it. So that will be a real challenge for the committee.

The other challenge I see is being able to include all the stakeholder groups that you might want. You have generic manufacturers. You have pioneer manufacturers. You have development companies. You have API manufacturers. You have drug-product manufacturers, whether they are conventional or sterile products. You have a lot of different audiences out there.

You have the biotech industry and can you get all the right people together in the same room and yet limit the number of attendees so you don't have a huge committee. So there are going to be some challenges. However, I do support the concept very strongly.

DR. LEE: Efraim?

SHEK: I would like to add a little bit of international flavor to it. In your background, Ajaz, you talk about the international cooperation. We know we have the ICH, of course, going on. But I believe it would be very nice if this subcommittee will have also this aspect. As with their guidance or regulations, science-based are being implemented, that the aspect of international harmonization should be taken into account as many of the companies are becoming global.

The world get smaller. It will be extremely helpful.

DR. LEE: Thank you.

Gloria? Gloria, by the way, is the consumer representative.

DR. ANDERSON: I have been looking through these papers I have here and I can't seem to find the statement of goals and objectives. Can you tell me where that is?

DR. HUSSAIN: The slide No. 4 was essentially the broad goals that sort of we proposed. Our initial thoughts were to use this committee to have input and advice to CDER FDA on science-based CMC and GMP policy development in the manufacturing area. That is the sort core

long-term aspect, but also continue development of the PAT initiative. Then, at least for certain aspects of the cGMP for the 21st Century initiative, itself.

So those are the three broad areas. I didn't call those goals but I think addressing, providing scientific input in those three areas are the goals.

DR. ANDERSON: I would expect the objectives to be a bit more specific. It is difficult for me to comment on them when I don't quite see them. I know what they are for the PAT committee and I think it is commendable that you are going to continue that. But it would be helpful to me if I knew a little bit more about specific detail regarding the objectives.

DR. HUSSAIN: If I may, I did not specifically identify that, but in terms of a bit more specifics, some of the topics for discussion, in my mind, one of the first topics was definitions and sort of common understanding of the terminology, the risk-based approach, what do we mean by risk-based approach in the manufacturing context.

I think we have different perspectives but

don't have a common understanding. So maybe one of the first topics we might pick up is defining these terminologies from different perspectives and sort of moving forward from there. That was sort of one objective, was clarity and definition.

The other objectives that I laid out in my presentation, itself, to start focusing on topics, approaches for enhancing the scientific basis for regulatory policies. An example that this afternoon we will start with that process is the aseptic manufacturing process, itself. So it is sort of staged.

We start out with maybe the fundamental basic definitions and then get into detailed topics for discussion. For those topics, we may need to bring a focused working group because the general, or the core membership of the subcommittee may not be the entire--have the expertise in all given areas.

So that is how we laid that out.

DR. LEE: May I turn the question back to you? What do you think ought to be the objectives?

DR. ANDERSON: I don't think I am in a position to do that. I think somewhere in the document that you have you have defined a problem

and out of that would grow the goals of the committee with some specifics as to how you would achieve those goals.

I usually look at goals and objectives in terms of what I hope to have accomplished at the end of whatever task I am doing. Of course, in my three years on this committee, it seems as if we have never gotten to the end of anything so that may be kind of difficult.

But I don't have any specifics other than those that relate to PAT which I am familiar with. I would be willing to talk with you about them rather than prolong this discussion.

DR. HUSSAIN: Many times, what we do is, for example, we came to fruition yesterday on blend uniformity. Essentially, that topic is completed. We discussed it twice at the advisory committee. The next step is guidance. So most of our end result generally is gathering information and then leading to a guidance document.

So, in the duration of, say, the last three years, if you look at--we finished the guidance on food effects. We finished the guidance on BA/BE. We essentially finished the discussion on blend uniformity. We finished the discussion on

polymorphism. So, in many ways, all these were completed projects.

DR. MEYER: In a sense, Ajaz, I am sure your immediate and intermediate steps are sort of the objectives of the committee.

DR. LEE: Would Gerry and Ken care to comment on the goals and objectives, what you would like to see as the goals and objectives of the committee?

MR. MIGLIACCIO: The four points that I put up are, certainly, from a PhRMA perspective what we would like to see the initial objectives of that committee. Again, to identify and prioritize the areas that require science-based GMP standards, to provide the manufacturing and quality perspectives on risk-based which, as Ajaz has pointed out, is something that needs definition.

Thirdly, to be involved in the technical issues resolution process as in a trend analysis capacity in a clarification of standards. Then, finally, to continue with the PAT model and focus on new technologies. So I think those are four key objectives for the committee.

LAVIN: I think what really should come out is a consensus type of document developed by

FDA and industry on what are the risks, what are the associated risks and what can we do to mitigate those risks. Our businesses are not in business to be noncompliant. That is not what our objectives are.

The FDA does not want that. We don't want that. As an American citizen and a consumer of those products, I don't want that. What we need is a clear set of directives or at least an open dialogue so that we can discuss these things instead of a hit-and-miss approach amongst firms, amongst districts, amongst investigators as well as between the districts and the Centers, themselves.

It is very confusing. Most have a handle on it. Most companies are dealing with that. But, just to be consistent in the approaches and what are the risks and mitigating those risks I think will go a long way to protect the American public.

DR. LEE: Well said. It seems to me the two words that cut across every area is the science and public-health protection. Science, as you know, always moves forward and, therefore, that is the standard is to move in pace with that.

So I think the goals and objectives are things still evolving that we kind of know in our

mind what they could be and I just don't think that we have the time to articulate precisely what those look like. So maybe that would be the first charge to this subcommittee is to clarify the goals and objectives for it. I think that we kind of have sufficient input.

Is there any other discussion?

DR. HUSSAIN: Two points. I think Judy raised a very important issue is the membership and representation. It is a very wide-ranging set of stakeholders and how do we manage that process. Efraim also raised an issue which I think is very important which is international cooperation. My experience with the PAT has been, because of the international membership on that group, in many ways, I think we have achieved harmonization without even talking about the harmonization process.

The reason is I think the science evolved incorporating the perspective from both sides of the Atlantic. So I think that is also a lesson learned and how do we capture that in this if we can.

DR. LEE: Very well. This is a proposal on the screen, two ACPS members. That is it on

this side of the table. And eight to ten expert members representing the stakeholders. Any comments about that?

DR. MEYER: Will FDA be represented, the A stakeholder, or--

DR. HUSSAIN: No; we don't count ourselves as part. We are here to listen and seek advice so we are not in one of those numbers there.

DR. MEYER: Who selects the working groups? These are, I assume, largely in addition to the eight to ten experts?

DR. HUSSAIN: We have some flexibility and we have different processes that we can do this. A subcommittee or a fact-finding group, we can actually appoint and select on our own. We don't have to go through a formal Federal Register process for that.

But, in the PAT subcommittee, what we had done was we had announced in the Federal Register a request for--we defined expertise and we invited people to participate. We had a very large number of applications that came in. So what we did in that case was select a core group and then we invited others who had applied to be a part of the different working groups. That is how we had done

that. But we don't have to have that restrictive process.

Kathy, do you want to say something?

MS. REEDY: The working groups are very flexible. The subcommittees are less so. Two members from the core committee is really the only requirement.

DR. KIBBE: That is a minimum; right?

MS. REEDY: Yes.

DR. LEE: I would like to follow up on what Marv said, whether or not there ought to be representation from the agency as some kind of a staff liaison.

DR. HUSSAIN: Could you repeat that?

DR. LEE: I think, in some organizations, you always have, let's say--let me point out the organization I know a little bit about is AAPS. There are a number of committees and each committee is supported by a staff member who is a resource. So that person is going to go get the information, get things done, that sort of thing.

DR. HUSSAIN: What we plan to do is we don't want to burden our Advisors and Consultants staff to that degree. So, what we have tried to do is try to help them--actually, with the PAT groups

and so forth, OPS has been providing some logistic support also so we will try to do the same thing. I think the Advisors and Consultants staffs are doing such a good job already, but their resources are limited. So we will have some other liaisons identified.

Marilyn is a liaison from OPS for this committee. We will create someone like that for the working groups and so forth, also.

DR. LEE: She is a superwoman.

Any other comments about this makeup, the two ACPS members?

DR. SHEK: If I may. One aspect, when you are going to make the decision look at the expert. I am looking at the title of the committee, Manufacturing. If you look at the goals, I think it is more CMC-type of a subcommittee. It is so purely, I believe, manufacturing.

As we looked, I think, at the experts, we should make sure that part of the stakeholders are coming from the R&D environment. Since they are basically GMP regulations from Phase I clinical studies, people are involved purely with the regulations. But there is also the aspect of the future and new technology coming in.

I think PAT is a good example where the push didn't come really from even R&D. It came from manufacturing, or not from the industry. In the future, it would be nice if we can turn it around. So, at least some of those eight to ten should come from an R&D environment.

DR. HUSSAIN: After I put the slide, it occurred to me I missed the R&D group. I just had manufacturing and quality assurance, but I think, unless you have the R&D part of that--I think it is important. Thanks.

DR. KIBBE: Just a couple of things. I think that this subcommittee has an opportunity in front of it to basically change the way both the Agency and the industry work in a lot of ways and have a long-term impact.

Changes could be advantageous for the industry in terms of efficiency, advantageous to the public in terms of better assurance. I am still struggling about making sure we have all the stakeholders and all the people involved and, at the same time, having all the expertise. It is clear that we need to have, at each one of our meetings, someone from the Agency that represents the field as well as someone from the Centers

because the field is going to have to activate what is going on at the same time.

It is clear that there are different concerns from different aspect of the industry but, at the same time, there are concerns from the people who are manufacturing testing equipment. We get a lot of good input in terms of PAT from them. And the international community that might be ahead of the curve on some things, behind the curve on others. I do respond quite positively to the comments that, while we were developing that, because we had an international flavor to it, harmonization came along as a consequence of fallout.

So I don't know how you are going to be able to pack all of that into eight people. I am worrying about making sure that we get the right mix and we have the right group, and then your time lines to get some of things done. We also need to get a real vision for the committee because of its potential large impact and goals and objectives.

It is going to be a daunting process the next couple of years.

DR. LEE: You might be the one we would ask to chair it, Art.

DR. KIBBE: I love daunting projects.

DR. LEE: As we discussed, the committee is extremely important and I think that we need to give it some careful thought about how to constitute it, to make sure it is a progressive committee. I think something I liked hearing this morning is that someone should be looking out to the future. Is that the charge within this committee? I think so. I think this should be looked at in order to mix housekeeping and forward-looking activities in the same committee is something that you might want to consider.

I am getting off the committee so I just would make a laundry list for my successors.

Any other suggestions? What does OPS expect from this committee?

DR. HUSSAIN: What we will plan to do is, in a sense, take the input and start working towards forming this committee and then go through the process that is needed to do that. Again, I think going through the PAT subcommittee helped because if you look, on my right, you have Doug and Joe always with us on the PAT so the process worked very well. I think we want to sort of repeat that success again.

Clearly, I think that this is not just CDER now. CVM, CBER and everybody--everybody has to be together on this. So it is a bigger challenge definitely than PAT, but I think going through that PAT process helped us at least create the part that will lead us to helping manage this more complex one.

DR. LEE: Just for clarification, Ajaz, the ACPS members are by statute?

MS. REEDY: Yes; at least two members.

DR. LEE: At least two; okay.

DR. MEYER: For the experts, do you have the eight to ten--do you have to have geographic distribution and ethnic distribution and gender distribution or can you pick eight females that are experts from Merck?

DR. LEE: What's wrong with that?

DR. HUSSAIN: We always try to go for diversity. That is always our goal. Definitely, I think that is mandated for the advisory committee, but I think it is a bit more flexible on that. But that is always our goal, to go for diversity as much as possible.

DR. LEE: Working groups.

DR. HUSSAIN: In terms of working groups,

I think what our thoughts were--for example, if I take the example of cleaning validation, it is a very focused topic. I think there is a need for guidance there. If I use that as an example, then the working group on cleaning validation would be sort of a fact-finding and making certain recommendations to the committee could be formulated and asked to do something rather quickly and come up with something, and so forth. So that would be an example.

But I think the numbers and the topics, I think I like what Gerry mentioned as part of the goal of the subcommittee is to identify these topics and prioritize them because there are many topics to be addressed. I don't think FDA has all the resources to start everything at the same time, so we have to manage that process well.

So one of the charges of the first meeting of this subcommittee would be to simply identify those topics, prioritize and then, as part of the goals and objectives setting itself. So that is how we intend to proceed.

DR. LEE: Gerry, did you want to make comments?

MR. MIGLIACCIO: I would be happy to

provide PhRMA's list of priorities to Ajaz to focus on. We have gone through that prioritization exercise. We have polled the entire PhRMA membership and I think there will be a lot of commonality from what you are thinking and what we are thinking.

DR. LEE: Anything else about the process?

DR. HUSSAIN: This is with the endorsement of that, and I think we can start taking input we have received and move forward.

DR. LEE: It is still not clear to me who is appointing the members. The OPS?

DR. HUSSAIN: We will work within FDA to bring that together. It will not just be OPS. It is the Office of Compliance and will involve other segments like Doug and other districts. So it is sort of a team process.

DR. LEE: Thank you.

Gloria?

DR. ANDERSON: I would just like to suggest that, prior to asking the committee, after you have formed it, to formulate the goals and objectives. It seems to me like someone would need to take a cut a doing a first draft because it is not clear to me how you will know what your

membership would look like if you haven't formulated clearly in your mind what the task is that the committee will do.

DR. HUSSAIN: In many ways, I think the manufacturing--the scope of the problem ranges from R&D to manufacturing to QA functions. So, in that sense, we think we have clearly identified what type of expertise and experience is needed.

I think the challenge would be the stakeholders because the number of stakeholders are many in the sense--I mean, we have two stakeholders represented here from the PhRMA and GphA but that is that is not a complete list of stakeholders. That will be a challenge, I think. That will be sort of an internal discussion and decision then.

DR. LEE: Evaluation.

DR. HUSSAIN: The evaluation, more I meant it--it is sort of reporting back to this advisory committee, itself. PAT kept receiving good timely feedback in terms of that. So it is continuing that process. If you have any thoughts on how we could have improved the PAT process, itself, that would be a sort of a question on evaluation on the PAT subcommittee, itself, from your perspective what we could have done better that will help us.

DR. LEE: Gloria?

DR. ANDERSON: I would like to suggest on the PAT, and this has always concerned me, is that I don't think we went back to the original goals and objectives enough to see where we were. At the last committee meeting, I suggested that now that we are as far along as we are with the task that was set out at the beginning, that it might be a good time to go back and see where we are and make some determination about how to proceed in the future.

I think that would be a good thing to do with this, particularly in terms of evaluation because I always look at evaluations as a means of determining the extent to which the goals and objectives have been or are being achieved.

DR. KIBBE: I think this particular committee is such a broad-impact full committee that we probably, after we get some general guidance from the agency on the overall mission or vision and begin to set goals and objectives, we are going to have to set milestones timely as we look at each aspect that we are trying to look at, if we are going to work in one particular area to start with and move through it.

I think Gloria is right. Closing the loop with advisory committees sometimes, as you said, "Well, we took all that information and guidances are coming." I think the committee would like to see the guidance when it actually happened so that we knew that what we did had an outcome that was tangible and useful.

Quite honestly, one of the things that I would like to see us do is survey our stakeholders independent of the committee for the impact of what is going on, maybe pre or post kinds of things, where we get a sense of what the industry thinks is happening today and then, two years from now what the industry thinks has changed and what has happened. That might be helpful, too.

DR. MEYER: A follow up on Art's comment. If I have a student prepare an exam for me and I grade that exam, I have evaluated them. But, if I don't show them what grade they have, they don't know how they did. I think that is missing to some extent in the activities of this committee. So if the subcommittees prepare something for this committee, this committee then talks about it for two days and Ajaz takes it and throws it in the basket, we would never really know that. It just

kind of disappears into the future.

It might be useful for the beginning of each session of one of these committees, or this committee, to have kind of a review; this said to this and this said to us and we thought it was a crock, or we have put forth a guidance.

DR. HUSSAIN: I think it is a very good point. In fact, it was raised yesterday. Dr. Lee is--sort of this is his last meeting and he has been the chair for a relatively short time. Some of the things we have started, he will not know what happened with them unless he comes back to FDA to find out.

DR. LEE: I don't want to know.

DR. ANDERSON: Also, I think as new members come in, I sort of look back at the memo I sent to you. I have the transcripts listed, the web addresses. But the transcripts may not always provide the summary that is need to keep the continuity. I think we will try to find some means of doing that.

DR. LEE: Very well. I think we have had some good discussion. I think the folks around the table probably will know exactly what to do. I think this is a very important subcommittee, an

experiment in extension. I emphasize that the basis is science, risk-based, quality and also I will add some common sense.

With that in mind, are there any questions before we take a recess? If not, let's continue at 10 o'clock. Thank you.

[Break.]

Manufacturing Issues

Sterile Drug Products Produced by Aseptic Processing

DR. LEE: We have some presentations on manufacturing issues, sterile drug products produced by aseptic processing. Ajaz, are you going to give the introduction?

Introduction

DR. HUSSAIN: My introduction is a brief introduction. Actually, I just wanted to introduce Joe Famulare. He is going to take the lead to introduce the topic. Just two perspectives I want to share with you. This is probably the first manufacturing topic in this format that we have brought to this committee so it is sort of a new format. Also, what we are trying to do here is to bring all segments of the FDA which impact on this topic.

So you are looking at Jay from CBER, Joe from CDER and Doug Ellsworth from the District representing those segments. The Office of Pharmaceutical Science, the Microbiology staff will make a presentation, a brief presentation, on how we are planning to support this initiative. So I think our goal here is to sort of listen to the Advisory Committee after they have a chance to listen to the issues being presented here.

So, with that, I will introduce Joe Famulare.

DR. LEE: Thank you.

MR. FAMULARE: Thank you and good morning.

[Slide.]

I just wanted to address this Advisory Committee to address the topic of aseptic processing standards today for a number of reasons. The most prominent of these is the urgent need to publish guidance that could promote better understanding of some basic cGMP issues relating to aseptic processes.

As we reviewed our program for the inspection of drug manufacturers from a risk-based perspective, we have agreed that sterile drugs are, in many respects, the highest risk category due to

the route of administration and the potential for hazard to the patient. Our 1987 guidance entitled, Sterile Drug Products Produced by Aseptic Processing, noticed that the Agency would issue revisions in the document from time to time when it recognized the need.

Through the regulatory efforts and comments submitted by interested persons, with this knowledge, the following evolution and technology stand as an understanding of aseptic processes, we embarked on the task of updating this 1987 guidance in 1997. The intention of the revision was to improve clarity and explanation of cGMP issues to better facilitate industry compliance.

[Slide.]

This effort, as Ajaz mentioned, is a joint CDER, CBER and ORA work product. We have here, of course, Doug Ellsworth representing the Field Drug Committee in ORA, the field, and Jay Elterman from CBER, the Director of the Division of Manufacturing of Product Quality in that unit.

The overarching goal of FDA in issuing revised guidance is to provide a document that will facilitate improved industry compliance. We receive questions on practical and technical issues

that have formed a clear pattern and plan to overlap very much with issues that are very often cited in regulatory citations, whether they be 483s or warning letters.

We want to bring clarity to these quality issues that are sometimes murky by providing sound understandable principles and without being overly prescriptive. We are providing this unprecedented opportunity for a preview of our current thinking because we believe it is urgent for guidance on aseptic processing to issue.

Thus, we have this concept paper here today to solicit feedback and we are trying to take in all the comments from this advisory committee in order to publish the draft guidance as the next step.

[Slide.]

Just to cover the concept paper, one of the basic things that we did was to improve the format over the 1987 Guidance. Hopefully, it is more user-friendly with a table of contents and headings and easy to read and follow. We have added definitions of air-lock components, colony-forming units, dynamic conditions, endotoxin, gowning qualifications, barrier and

isolator technologies, et cetera, so that we wanted to bring things in line with today's current technologies.

We have also updated old sections. One of the areas, of course, would be the evolution of the sterility testing in the USP. And we have added some new sections, again based on advances of technology and dealing with issues that we see as needing the most guidance such as personnel, the use of isolators and early processing steps are particularly a concern to the biologic industry.

[Slide.]

This guidance has been requested by the industry. Again, we hope to promote better understanding of GMPs. Industry organizations such as PhRMA and PDA have requested updating guidance on an expedited basis to address areas where there is confusion on what the minimal GMP standards are. FDA, of course, agrees that we wanted to provide this guidance.

By having proactive communication of our expectations, we hope for firms that are building or modifying facilities to do that in an efficient, money-saving way, and to, again, clarify issues where questions persist.

[Slide.]

In answering the question why to improve the guidance, it is important to reflect the evolution of knowledge, remove that information that is obsolete from our 1987 Guide that is out there, and fill major voids that have been illuminated over time. We want to reflect current standards and, importantly, we want to incorporate the latest scientific principles.

[Slide.]

We want to reflect uniformity between the Discussions and Biologics Center and, of course, have the field represented well in terms of the implementation by field investigators in looking at aseptic process manufacturing. We want to move forward on those issues that have been debated year after year in working together on new matters of importance so that the most important issues are covered during our inspections and are given emphasis by companies.

[Slide.]

Going back in a little bit of history, the original 1987 Guidance was written in lieu of regulations and the process began, really, around 1980. In the Preamble of the GMP regulations of

1978, it said that, while the GMP regulations address finished dosage-form drugs, that many unique and critical variables attendant to sterile drug manufacturing would be best addressed thought the publication of additional regulations on both SVPs and LVP; that is small-volume parenterals and large-volume parenterals.

Most of you know that FDA ultimately wrote regulations for LVPs but they were never finalized. In lieu of the regulations, of course we provided the Aseptic Processing Guidance of 1987. The choice of the guidance route, we hope provided industry with a better understanding of FDA's interpretations of the regulations while still leaving significant flexibility for manufacturers by virtue of not establishing mandatory standards.

That 1987 guidance, we believe, proved effective in answering some recurrent questions at the time but, over the last several years, we have recognized the gap of updated cGMP guidance in high-risk areas of sterile drugs. Industry representatives have repeatedly asked for the issuance of this document since our inception of announcing that we were working on this.

[Slide.]

It is important to address the quality of sterile drugs as a priority for the Agency. One of the reasons that, of course, this ends up as being one of the first things that we look at, as we look at the formulation of this new manufacturing subcommittee. We see that there are persistent problems that need to be resolved and averted in the first place.

It is very important to maintain a steady supply of many of these drugs to the American public. We see that they represent very important therapies. Very often parenteral manufactured products end up being areas where we have shortages and there has certainly been publicity in the recent year or so, whether it be certain biologic products such as flu vaccine and other types of vaccine products that not only are important therapies but are also national security concerns.

So it is important to have this area covered in a way to avert these problems in the first place. Of course, handling these in the regulatory mode is a time-consuming problem for both FDA and the industry.

So we are hoping to have better adherence to cGMPs for sterile products through improved

guidance, improved inspectional focus and better understanding of the scientific principles.

[Slide.]

We could see, in looking at the recalls from Fiscal Years '99 through 2002, that certainly lack of sterility assurance has represented a large number of recalls that have occurred over these last couple of fiscal years so, again, reinforcing the need to avert these problems and to find out what the problems are in advance and to work through this guidance in identifying those areas where we could give the best guidance to avert these types of problems.

Many of these result as an outcome of cGMP inspections. You can see, just looking at Fiscal Year 2002, we ended with some 52 recalls in this particular area.

DR. MOYE: Could I ask just a clarification while that slide is up? What do the colors mean?

MR. FAMULARE: They just distinguish the different years.

DR. MOYE: They were all blue except for the last two.

MR. FAMULARE: There is no other meaning

other than to distinguish the two years. I apologize for not having a consistent pattern of thought for the colors.

DR. MOYE: That's all right. I just didn't want to miss anything.

DR. KIBBE: Is there an explanation for the dramatic change between '98 and '99?

MR. FAMULARE: Many of these result as a result of cGMP inspections that have occurred. In one particular instance, and this is top of my head, I think one company that was under a regulatory concept decree actually cleaned up the marketplace of their products rather than to try and evaluate all the different sterility problems that may have occurred from products that they were, overall, eliminating from the marketplace.

So, as a matter of expediting removal of suspect products, the company removed them all and each product represents a separate recall incident. So it is not companies, per se, but individual products.

Any other questions on this slide?

[Slide.]

Important to consider for aseptic processing is that there are many variables that

occur in aseptic processing. So, in preparing this guidance, we had in mind that aseptic processing requires daily vigilance and attention to many details which is certainly a true test of cGMP conformance.

Adherence to procedures and details is important and fundamental to sterility assurance. Process consistency in aseptic processing is of utmost importance. An overriding objective, of course, is that each unit produced in a batch be free of microorganisms.

In looking at sterile drugs, in terms of our risk-based approach, as Ajaz mentioned in looking at the goals of the cGMPs for the 21st Century, as a product class, of course, sterile drugs can represent hazards to a patient and an unacceptable risk to patients that may be posed by contaminated drugs.

[Slide.]

Failure to adhere to cGMPs in the instance of aseptic processing can have an impact on product safety and efficacy and, therefore, this whole category of drugs is a top priority for inspectional coverage is a risk-based inspection approach.

[Slide.]

In looking at the risk-based approach, we need to analyze what are the causes of contamination and where are the potential roots of contaminations in a firm's process. We need to focus in our guidance on the issues of most concern, those critical control points. So these are the areas that we will be looking for comment as individuals have looked at the concept paper that we have put out there to see that we have put proper emphasis on these issues of most concern.

[Slide.]

Good science, of course, again, a recurring theme of today in focussing on these issues. We want to have a scientific-based approach to cGMP emphasized in the concept paper. In putting together this paper, there were certain key sources that were looked at; scientific journals, technical documents, various textbooks, vector illuminated by facility-contamination findings when we actually had the opportunity, as FDA investigators or even as people in the Office of Compliance that review the results of these investigation reports, have actually had hands-on experience in seeing what the results of those

investigations are and what the findings of contamination have been.

Very importantly, we hope to have captured within this document the results of our cGMP case reviews and the many cases that we have looked at, both particularly CDER and CBER, at our level, to see what the commonalities were, to see what those areas of emphasis need to be which led to our regulatory entanglement so that we could take that experience and bring it forth into this concept paper and eventually into guidance to address those issues.

[Slide.]

I will just briefly--Ajaz went over this in great detail this morning--the cGMP for the 21st Century to make sure that, as we look at this concept paper that will eventually be our guidance, that we outline the risk-based approaches that will better focus FDA's and industry's resources, we make, as is noted in this concept paper, a good system better, focus on critical process parameters, critical control points and yet be flexible enough to encourage innovation in the industry.

So, while these are the major goals of the

cGMP for the 21st Century Program that was announced this past August by the agency, we want folks to keep this in mind in looking at the concept paper, that we keep sight of theses goals as we put forward our ideas in this concept paper.

[Slide.]

We have to recognize the diverse nature of the industry and that new guidance will address this essential practicality while also providing meaningful insight into what FDA's expectations are. We need to encourage innovation by acknowledging new technologies and by liberalizing some old standards where it is appropriate.

For example, in one of the examples that I could think of in the concept paper where we had a specific number for the rate of air flow, now this could very often be demonstrated by smoke studies. It is important to remember, again, and I know we say this every time FDA issues a guidance but I will emphasize it again, that this will be a guidance and not a regulation so there is latitude for flexibility.

[Slide.]

So, to focus on today's broad question in looking at this concept paper. What additional

considerations are needed to ensure that the proposed guidance contributes to the improvement of the aseptic manufacturing process across the industry, improves consistency in the FDA inspection process, and, at the same time, can encourage innovation in the aseptic-process manufacturing arena.

[Slide.]

Continuing our broad questions, is FDA's current thinking on these topics as outlined in the concept paper well grounded in science and sufficiently detailed to provide industry with clarity on FDA's expectations with respect to assuring appropriate quality of sterile drugs by aseptic processing?

[Slide.]

We see, again, a compelling need for this revision to the 1987 guidance. The concept paper represents our current thinking to date and we really value your feedback, particularly on the level of specificity. There is always debate as to whether we have targeted what we are looking for too specifically and, at the same time, allowed latitude for individual innovation or individual firms' needs.

We will listen carefully and do a comprehensive review of all the advisory comments and, of course, then we will take this advice and be able to put this best effort as the results of the comments we get from the advisory-committee setting here today into publishing a draft for public comment.

I just want to end by thanking all the internal constituents within FDA that have worked very diligently. As you see, the project started in 1997 in order to gain a consensus within FDA to put out this concept paper. Those are the various groups with CDER, OPS and OC, ORA and CBER.

Thank you.

DR. LEE: Thank, you, Joe.

Any immediate questions?

DR. HUSSAIN: Joe, if you want, or I think we need to introduce the invited guests to this section.

MR. FAMULARE: Okay. We will have, as speakers, and I don't have the names in front of me except right over here, various representatives of the FDA to introduce various topics or subjects throughout the day. But we also have some invited guests such as from the PDA, Russ Madsen who will

be talking this morning, giving the PDA perspective.

We have Berit Reinmuller who will be giving a technology presentation on air flow and air velocity. And then we will have various FDA individuals really serve to structure the topics of the day. Actually, the next presenter will be Rick Friedman who will set the stage for the various issues, the five main issues, that will be covered out of the guidance.

Not to steal his thunder, I will let him introduce those topics, but he will be the first speaker broadly introducing those topics. He will be back again this afternoon to introduce one of the five topics along with Kris Evans from ORA, Bob Sausville from CBER and Brenda Uratani from CDER Compliance. Again, representing the collaboration on this document, we will have from OPS, from the review side, also giving a brief presentation on the interrelationship of the review and the GMP side, David Hussong.

Did I forget any names, Ajaz?

DR. HUSSAIN: Also, I think if you could just go around the table and introduce the new invited guests, also.

MR. FAMULARE: Okay.

DR. LEE: Or we could have them identify themselves.

MR. FAMULARE: Oh; the other guests? I don't have the list in front of me. Those guests. That would be easier just because I don't have the names in front of me. I'm sorry.

MR. MUNSON: Terry Munson. I am a consultant from KMI/Parexel. Was ex-FDA, worked in the Office of Compliance at CDER.

MS. LOWERY: Sandi Lowery, a consultant from Quality Systems Consulting.

DR. BURSTYN: I am Don Burstyn from Alkermes Pharmaceutical Developer and Manufacturer.

MS. DIXON: I am Ann Marie Dixon from Clean Room Management Associates. I am a consultant.

DR. KORCZYNSKI: Michael Korczynski, Principal, Mikkor Enterprises.

DR. LEE: And Professor Reinmuller from Stockholm?

DR. REINMULLER: Berit Reinmuller from the Royal Institute of Technology in Stockholm, Sweden.

MR. MADSEN: Russ Madsen from PDA.

DR. LJUNGQVIST: Bengt Ljungqvist, from

the same university as Berit Reinmuller.

DR. LEE: I think that covers just about everybody before lunch. Thank you.

MR. FAMULARE: Rick Friedman will be the next presenter. One of the other guests is Jeanne Moldenhauer.

DR. LEE: It is hard for me to keep track of all these names.

Rick, you have twenty-five minutes.

Contamination

MR. FRIEDMAN: Thank you and good morning. My name is Rick Friedman. I work for the Center for Drugs, Office of Compliance.

[Slide.]

Aseptic processing is an intricate and complex method of producing sterile medicines. Since the publication of the 1987 Guidance Document, there has been an evolution in the knowledge and understanding of aseptic processing. Data-analysis experiences shared through pharmaceutical-industry publications and conferences have contributed significantly to this enhanced understanding.

CDER, CBER and ORA have issued a joint concept paper for your consideration that

comprehensively outlines the cGMP areas that we believe are in most need of guidance. The cGMP specifically addressed the need to monitor and control sources of variability in the manufacturing process. GMP representatives throughout FDA regularly speak of identifying the critical control points for a given process and the need to support the process with well-conceived design control and maintenance procedures.

Using this mind-set of sources of variability and critical control points, our concept paper stresses major indicators of quality for an aseptically processed parenteral drug.

These key determinants of sterile drug quality also make up the main theme of this presentation which will provide a bit of the theory and practice that have formed the foundation of our current thinking.

After discussing some of the science base, I will address the practice through sharing a few case studies that illustrate where one or more critical control points failed with the consequence of nonsterility.

[Slide.]

It is very difficult to quantify risk but

there are a number of useful tools in the literature describing metrics often used by the pharmaceutical industry. One method is discussed by Paul Noble in the July or August 2001 PDA Journal. He uses the popular failure mode and effects analysis, FMEA, method to indicate which parts of a firm's operations present most GMP and public-health risk and, therefore, deserve the greatest attention.

In discussing the three aspects of this method, he starts with the first component, reducing the severity of risk by process changes or product redesign. He states an example of reducing risk severity would be exploring development of a terminal sterilization process for a product that is aseptically produced.

The second component of this method is reducing the probability of occurrence of risk. Noble states that these improvements can have "long-lasting benefits" including efficiency gains and avoiding future problems. He names the following systemic improvements; "process automation, tighter controls upstream in the process and implementing new technologies such as isolators to reduce the chance of microbiological

contamination."

He then discusses the third category, the detection of failures. He characterizes validation tests as "intensified monitoring"--that is a great definition of validation--"which should detect flaws or weaknesses which may not be normally observable. A media fill is a good example of a validation test."

He notes that, "Conducting a medial fill will not, by itself, reduce the chance of contamination. Only a proper corrective action response to the detected flaw or weakness will do so." We found it notable that these examples named by the author as beneficial in preventing the costs associated with product-quality problems also happen to mirror the many principles included in our concept paper and these issues will be among our major topics of discussion today.

[Slide.]

Our revision of the aseptic-processing document began by asking this basic cGMP risk question; what are the potential sources of contamination in an aseptic process? In an effort to answer this question, the concept paper focuses on selected aspects of the aseptic process and

facility that, if not maintained in a good state of control, can lead to the contamination of finished units of a parenteral drug.

We also asked the question, what measurements are most valuable in indicating sterility assurance. While cognizant that some factors of the manufacture of a drug are more influential than others, they get different weights, we acknowledge what so many before us have also acknowledged, that, if an aseptic-process operation does remain in control throughout processing, contamination may occur that is unlikely to be detected in the end-product sterility test of a very small number of units.

Instead, there are number of personnel, environmental and mechanical variables that must be considered to make a reliable assessment of whether the aseptic operation is under control.

We also concluded that such metrics should be founded in scientifically sound in sufficiently representative sampling plans so that meaningful data can be used to evaluate whether a batch was produced under adequate conditions. We felt that we should focus on those metrics that can provide a signal of an emerging or existing route of

contamination.

In short, our compound addresses areas of GMP that, if not controlled, can impact on drug safety and efficacy and we will not need to go into explanation for the group assembled today regarding the fact that parenterals contaminated due to poor manufacturing conditions have, in fact, led to infections.

[Slide.]

This slide is an attempt to visually illustrate the complexities of aseptic processing. One might call it a macro-model of daily "sterility assurance," and sterility assurance is in quotes because we know the difference, obviously, between SAL, sterility assurance level, which is predictable in internal sterilization and the vagaries of aseptic processing.

This macro-model of daily "sterility assurance" includes the big-ticket facility and process-control factors that form the basis of overall process control. The first influential cGMP element is personnel--I will go around clockwise and maybe give an example or two quickly--but, personnel, facility and room. The D and M mean design and maintenance. The kind of

question we would ask from a GMP perspective is is the facility constructed to accommodate the constant dynamic interaction between rooms and does the design create contamination routes. Is an adequate maintenance program in place to address the gradual breakdowns in facility infrastructure.

Aseptic processing line design and maintenance process--this refers to both the filling process and the unit-sterilization operations that support it, autoclaving, et cetera, dry-heat depyrogenation. Does personnel and material flow through the facility increase the chance for tracking contaminants into the aseptic-processing room? Do the ergonomics of process flow or equipment configuration create difficult aseptic manipulations, unnecessary activities too close to the aseptic zone or other issues which undermine confidence in the sterility of each unit?

HVAC and utilities; response to deviations and environmental control trends; disinfection regimen and actual practices, media fills; and, of course, the essential role played by the quality assurance and quality-control units.

[Slide.]

So there are a number of potential sources of contamination that must be addressed in accord of cGMP. The existence of these many interdependent sources of variability are succinctly summed up in this excerpt from ISPE's Sterile Facility Guide which emphasizes that the aseptic-processing room does not exist in a vacuum. The room is part of a dynamic integrated system that is affected by the activities that take place both within it and around it. As such, they write that a firm must employ, "a strict design regime not only in the process area but the interactions with surrounding areas and movement of people, materials and equipment so as not to compromise aseptic conditions."

In other words, the microcontamination can eventually migrate to the critical zone and cause product nonsterility if attention is not paid to the holistic design, control and maintenance of the facility.

[Slide.]

There will be a lot of discussion today about environmental-control design and, of course, personnel. So let's look closer at some quotes from journals and textbooks of the topics of

personnel design and environmental control. Even with a good facility and processing line design, poor personnel practices can upset the delicate balance of the aseptic operation. With regard to aseptic interventions, our '87 Aseptic Guidance points out that any manipulation of the sterile dosage-form containers and closures involves the risk of contamination and, thus, must be carefully controlled.

The late Professor Kenneth Avis of the University of Tennessee spoke about the need for "continued vigilance throughout the entire manufacturing process" back in 1971 in the PDA Journal. The researchers Ljungqvist and Reinmuller state, in their textbook, Minimizing Contamination Through Proper Design, that, "Unstable situations are, in most cases, caused by the influence of arms and hands."

We are pleased that Ljungqvist and Reinmuller, whose research has been widely cited by industry and regulatory authorities alike could travel here from Sweden to discuss their research today. They have made a significant contribution to parenteral science in their studies of the influence of design, personnel practices and

environmental control on product contamination.

[Slide.]

Here are a couple of references on environmental control. Let's look at the second one. Sinclair and Tallantire performed studies to determine if a correlation between Class 100 control and contamination prevention exists. Using a blow-field-seal line, BFS line, and a known microbiological challenge level, this research team established that there was a "definable direct relationship between the fraction of product contaminated in the lot and the level of microorganisms in the air surrounding the machine."

This type of basic research study is useful in that it showed a correlation between an increasing number of microcontaminated units and the degree of contamination in the immediately adjacent machine containment room.

[Slide.]

Among the recommendations was that local protection of the operation could be improved to make contamination risk to the filling step more independent from the adjacent operation, the adjacent environment. Sinclair and Tallantire also found that product protection at lower velocities

was inadequate to prevent contamination. As velocity increased in this system, the number of nonsterile units decreased.

They conclude, for the systems studied, "a reduction in contamination of blow-field-seal product is achieved by a 'high-quality and high-volume air shower to protect the filling zone.'"

I have just reviewed just some of the numerous useful references that are relevant to our discussion today. Based on these and many other references, there is concrete foundation in the Year 2002 for the statement that, "Design, environmental control and personnel practices are each crucial to an aseptic processing operation."

You might ask, at this point, how does this statement of theory correspond to our actual experiences with industrial-contamination problems? The answer to this question is that we see a cross-section of sterility failures each year that illuminate commonalities in the source of contamination. Lack of adherence to cGMP in one or a combination of these three areas has been central to the vast number of these.

This brings us to some case studies that

illustrate the origins of some of these contamination problems. Some have asked the question, what makes three validation batches so special. Why not one, or five or ten? A three-lot study may, indeed, not be perfect but it does generally provide a reasonable degree of reproducibility given practical and business limitations.

A commercial process is tested with three different lots, each with their own unique variables presented by a given day in it is somewhat unpredictable events and, if done well, at the conclusion of the three-batch study, a more enlightened understanding of the state of commercial process control will be gained.

[Slide.]

This case study is a good illustration of the value of showing reproducibility. In this case, a firm had a pristine clean facility for two or three years, no media-fill failures. It is a large manufacturer. And then, one day, it had a media-fill failure where approximately 60 percent of the vials were contaminated.

The failure was considered to be a spurious event. Nonetheless, there were some

corrections that were made to the firm's satisfaction to improve different areas which were thought to, in fact, correct the issue.

The firm looked at the FDA guideline and PDA's Technical Report No. 22--both note that three lots are needed if a line falls out of qualification--for revalidation. So they ran the first media-fill batch and found no contamination.

They ran a second media-fill batch and this one was over 95 percent contaminated over 5,000 vials. The third media-fill batch was run. No contamination. So, one can see, if one batch was run, a firm would return to production and release of commercial lots without knowledge that a nonsterility problem still existed.

The root cause in this case had to do with personnel. Isolates in both failures, both of the media-fill failures, were common skin-borne microbes. They found that the gowning level was inadequate. Part of gown was nonsterile and the sleeves were sterile and maybe other parts of the gown were also sterile. But part of the gown was nonsterile and they felt that the aseptic technique was questionable and there was also some skin exposed.

Now, work was being done under a hood so presumably, by doing the work under the hood with sterile sleeves and sterile gloves, there wouldn't be contamination. But, obviously, this underscores the importance of full gowning and the fact that touch contamination and cross contamination from nonsterile and sterile parts of the gown is a practical reality.

The corrections to resolve these issues in this case were enhanced personnel and environmental monitoring performed in the near term. But the firm did, and one of the things that we are stressing in this guidance, increase in automation, removing personnel as much as possible from the aseptic processing by later modifying the line to allow for sterilization in place. They no longer have an aseptic connection. So they have taken that risk out of the process.

[Slide.]

This recent case study occurred at a major manufacturer, also. During the inspection of this facility, the inspection team actually entered the clean room on a nonproduction day and found mold in the aseptic-processing room. Mold had built up in between two walls in which the return vent was

located.

The investigators observed a significant area covered with greenish hard, dry mold drippings that extended out of the vents. It was evident to them that this visible mold buildup in the air returns should have been readily noticed and it appeared that it had been there for quite a while.

The firm had validated a number of sterility failures without an adequate basis, a laboratory causality. In addition to the highly unusual event of our investigators seeing the mold in the room during the inspection, the firm had detected a clear adverse trend showing persistent mold contamination in the area during environmental monitoring. The firm had a trend of several sterility failures and the inspection team found that the same molds found in the environment were also named as isolates in the sterility test positives.

[Slide.]

Here is an abbreviated summary of some more cases where adequate procedures were not followed to prevent microcontamination. The origins of contamination listed on the next two slides are those named in the firm's actual written

or media-fill and sterility-failure investigations.

Just to go through these quickly. Aseptic practices is named very frequently in media fill and sterility failures. Personnel returned after a long winter shutdown. We have seen this scenario repeated a few times over the years. There might not be the currency of knowledge coming right back from a one or two-week vacation and the recall of the importance of vigilance in aseptic technique. In this case, that was the attributable cause.

[Slide.]

In another case, an operator reached over open vials to remove a fallen vial on the line with gloved hands. This was observed and it was a common practice. This was considered to be the cause of the failure. Poor personnel flow has also been named in media-fill and sterility-failure investigations.

Poor aseptic connections; I just gave an example but we have seen that many times just this year. Poor sanitization procedures deficient or poorly executed; I have never seen more cases of that than in the last year. Construction in another room of the same floor of a facility caused increased airborne contamination. This has

happened a number of times. It is well-established in bioaerosol and other textbooks including the Macular Textbook of Aerosols showing that when there are construction facilities, mold can be widely dispersed in the facility and make it to places you would never expect it to make it.

In this case, a Bacillus was the contaminating organism. There is a specific species that made it all the way down the lengthy hallway through the aseptic-processing facility airlock--that hallway was uncontrolled because it is part of the office environment, et cetera--through the aseptic-processing facility air lock--now, you are in aseptic facility--into other clean rooms, into the aseptic-processing room, finally to the aseptic-processing line to the critical zone and into the product, all the way across the facility where construction was taking place.

There have been a number of sterility failures in a several-week period with this isolate in the product that coincided with the construction. The environmental monitoring showed an atypical trend of this organism and the firm concluded migration of spores from the area under

construction was, in fact, the root cause of the sterility failures.

[Slide.]

Another case, a new line was put together, installed. An HVAC was installed. The line was signed off as qualified, the HVAC systems, signed off as qualified by everybody involved with the validation and qualification report. But, to prove out that this process actually was in control, they did what firms do when they have major changes, as again recommended by PDA and FDA, they did a media fill. The media fill demonstrated inadequate HEPA seal and, over 90 percent of the vials in the batch were contaminated.

Velocity through HEPA filters. It has happened a couple of times in the last few years. I will tell you one quick story. In the case detailed on this slide, the firm had replaced a fan and installed the wires with reverse polarity so the fan ran backward and counteracted the other fans in the HVAC unit.

This problem was not detected by facility monitoring systems including a probe that was monitoring pressure drop across the filters and there was no check of velocity at the time to

confirm that the installation went well because a like-for-like change was not considered to be significant in the change-control procedures.

The firm ran for three months under these conditions. When they ran a media fill, they found eleven contaminated units in about 18,000 vials. They attributed the failure to velocity problem.

Finally, there are a number of cases where we have seen mechanical failures of filling tanks, main-pump failure, cooling system, leaks at joints or pin holes. All of these have been named in field alerts and in media-fill and sterility-failure investigations.

[Slide.]

With this background, we have worked to update our Aseptic Processing Guidance to address persistent areas of cGMP deficiency. Clarifying basic cGMP expectations will be beneficial to all of us in promoting uniform interpretation of a number of big-ticket issues that are unnecessarily murky. This advisory committee meeting provides FDA with an excellent opportunity to receive feedback on our aseptic-processing concept paper on these five important topics; sterilization options, aseptic-processing-design evaluation and

contamination prevention, media fills, environmental monitoring and personnel issues.

[Slide.]

I will close, in the last couple of slides, with just some specifics on the contemporary cGMP philosophies behind our concept paper. One of the main objectives was to recognize the advantages of new technology, automation and facility improvements. For instance, the compound acknowledges benefits of isolator technology by stating that isolators appear to offer and advantage over classical aseptic processing including fewer opportunities for microbial contamination during processing.

So we are noting the tangible improvement afforded by isolator systems as well as acknowledging the lower gowning requirements, lower clean-room classifications and the ability to campaign, which is a departure from the old twenty-four-hour turnaround manufacturing paradigm.

We also emphasize the need for a well-conceived design. For example, we discuss the use of air locks to provide better aseptic-processing-facility control. While stating that air locks are useful in multiple places, the